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Change in access blood flow over time predicts vascular access thrombosis

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Background. Vascular access thrombosis accounts for at least $1 billion dollars in annual expenses and 25% of hospitalizations for chronic hemodialysis patients. Low vascular access blood flow (less than 800 ml/min) has been shown to modestly increase the relative risk for thrombosis in the subsequent three months. In this study, it is hypothesized that a time-dependent decrease in vascular access blood flow may be more predictive of subsequent thrombosis especially in vascular accesses with flows more than 800 ml/min, since it would indicate the development of a critical outlet stenosis in the graft.

Methods. Ninety-five accesses in 91 CHD patients were prospectively followed over 18 months. Vascular access blood flow was measured every six months by the ultrasound dilution technique. Thrombotic events were recorded during the three study periods.

Results. A total of 34 thrombotic events in 95 accesses were documented through the total study duration. Accesses that thrombosed had a 22% decrease in vascular access blood flow during the first observation period and a further 41% decrease during the second observation period as compared to 4% drop and 15% increase during the first and second observation periods, respectively, for accesses that did not thrombose. There was an estimated 13.6-fold (95%, confidence interval 2.68 to 69.16) increase in the relative risk of thrombosis for accesses with more than 35% decrease in vascular access blood flow compared to those accesses with no change in blood flow. There was no statistical difference in the average vascular access blood flow of all patients over the study period.

Conclusions. Accesses that show a large (>15%) decrement in vascular access blood flow are associated with a high risk of thrombosis. Serial measurements of vascular access blood flow predict access thrombosis.

Vascular access failure represents a leading cause of morbidity in the chronic hemodialysis (CHD) population, being responsible for approximately 25% of all hospital admissions. According to the 1997 U.S. Renal Data System Report, Medicare paid for 73,000 hospital admissions and 123,000 outpatient procedures for vascular access-related problems in 1994, with an estimated annual hospital-related cost approaching $1 billion per year [1]. The high level of hospitalization is a consequence of unanticipated thromboses and generally results in surgical or radiological intervention for removal of the thrombus and repair of the attendant stenotic lesion.

The most common cause of thrombosis in polytetrafluoroethylene (PTFE) grafts is progressive stenosis of the venous outlet associated with myointimal proliferation [2]. Recent evidence suggests that when combined with therapeutic interventions, prospective screening and detection of dysfunctional hemodialysis accesses may reduce the thrombosis rate and improve its long term patency [3–5]. These findings have led to recommendations for using a series of indicators that ostensibly detect stenosis at the venous anastomosis prior to the development of thrombosis. These indicators include increased "venous" or dialyzer efferent pressures [6], intra-access pressures at zero dialyzer flow [7], urea recirculation, unexplained decline in the dose of dialysis [8, 9] and vascular access blood flow (VABF) [4].

Among these purported indicators, VABF has been recently shown to be one of the more sensitive measures of vascular access dysfunction. Access blood flow can be measured using several techniques including Doppler ultrasonography [10–12], magnetic resonance [13] and ultrasound dilution [4]. High cost and operator dependence have limited the utility of magnetic resonance and to some extent, Doppler ultrasonography. Ultrasound dilution [14] is a new method that has been shown to reliably measure VABF and has been extensively validated for this purpose. In a recent prospective study, our laboratory have shown that VABF is a useful indicator of subsequent vascular access thrombosis in PTFE grafts using either Doppler ultrasound or ultrasound dilution [15]. Specifically, VABF

Key words: hemodialysis morbidity, blood flow, stenosis, ultrasound dilution, hospital admissions, polytetrafluoroethylene grafts.

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Table 1. Demographic characteristics of the study population

Gender (M/F)	53%M/47%F
Race	32% White/68% African-American
Age *years*	57.6 ± 11.4
Cause of ESRD	30% Diabetes
	46% Hypertension
	4% Glomerulonephritis
	4% PKDA
	16% Unknown

Table 2. Vascular access characteristics

Access type	76% PTFE grafts
	24% AVF
Anatomic location of access	44% Left lower arm
	27% Left upper arm
	13% Right lower arm
	16% Right upper arm
Configuration of PTFE	90% Loop
	10% Straight

less than 800 ml/min was associated with significant increase in risk of thrombosis in the subsequent three months. In that study, as well as in another preliminary study [4], the data analysis was restricted to a single time point measurement of VABF and the subsequent risk of thrombosis in the following months. Nevertheless, the increase in the relative risk of thrombosis for VABF less than 800 ml/min was modest, primarily because a number of patients with access blood flows greater than 800 ml/min also thrombosed and a few patients with VABF less than 800 ml/min did not thrombose in the subsequent three months. In the current study, we hypothesized that in addition to a low access blood flow, a time-dependent decline in VABF may also be predictive of the development of a critical stenosis and a higher thrombosis risk. We therefore prospectively studied the association between changes in VABF and subsequent thrombosis by serially measuring VABF in a cohort of CHD patients with baseline VABF levels higher than 800 ml/min.

METHODS

Patient characteristics

A total of 91 CHD patients at the Vanderbilt University Medical Center outpatient dialysis unit were surveyed initially for the study. At the first measurement of VABF, 27 patients were found have VABF less than 800 ml/min. Since those accesses are already at high risk for subsequent thrombosis based on our earlier published study [15], they were not included in analysis. Demographic characteristics of the patients are presented in Table 1. In general, the study group is reflective of the ESRD population in the United States. All patients were dialyzed with biocompatible membranes (F-60, F-80, F-8; Fresenius, Concord, CA, USA) three times per week using the volumetric controlled dialysis delivery system, Fresenius 2008H. Patients were anticoagulated using heparin with an initial bolus of 75 U/kg and 500 U/hr that was turned off one half hour before the end of the treatment.

Vascular access characteristics

Ninety-five permanent vascular accesses, either polytetrafluoroethylene (PTFE) grafts (76%) that were at least four weeks old or native arteriovenous fistulas (AVF) (24%) that were at least 12 weeks old were included in the study. Baseline characteristics collected for all accesses studied including type of vascular access (AVF vs. PTFE), anatomic location (left or right arm, upper or lower arm) and configuration of PTFE grafts (loop vs. straight) are shown in Table 2. During this period 58 accesses were evaluated three times at six months apart, and 27 accesses were evaluated twice. Four patients had two vascular accesses evaluated during the total follow-up time of the study. The remaining 10 accesses developed irreversible thrombosis after the first measurement of access flow and thus were not included in the analysis.

Study design

The study was of prospective cohort design over an 18 month period. Vascular access blood flow and recirculation were measured utilizing the ultrasound dilution technique (Transonic Systems, Inc., Ithaca, NY, USA) at 24 week intervals for a total of three consecutive measurements. This technique has been extensively validated both *ex vivo* and *in vitro*. The measurement was done within the first one half hour of the dialysis session for each patient at a blood flow rate of 400 ml/min. For each study period, measurements in all patients were completed within a window period of two weeks. All patients were then monitored for thrombosis and then followed for events over the subsequent 22 weeks. To be able to document thrombotic events as accurately as possible, data were obtained from different sources: (*1*) scheduling notebook for the operating room, (*2*) log book for access malfunction in the acute dialysis unit, (*3*) operating room procedure registry, (*4*) the procedure logbook of the angioplasty suite at the Radiology Department, (*5*) obtaining history from patients, (*6*) Computer Medical Records Data System, and (*7*) medical charts. No specific protocol to correct access malfunction such as angioplasty or surgical revision was in place during the study period.

Statistical analysis

For univariate analysis, tests of hypothesis concerning between group comparisons were made using the mixed effect analysis of variance (ANOVA). For lifetime data analysis, distributions of times to events were estimated with the method of Kaplan and Meier. The PHLEV SAS

macro for proportional hazards model analysis with multiple observable vectors for the same subject [16] was used to adjust the intracorrelation effect for the patients who had multiple thrombosis. This procedure is a repeated measures analysis for correlated time to event follow-up outcome and a set of predictors. The statistical test results from the PHLEV SAS models were consistent with the results from the log-rank test. Because of the very small number of repeated events within the subject, the statistically consistent results from both methods were not unexpected. For multivariate analysis, the Generalized Estimating Equation (GEE) method for longitudinal data analysis [17, 18] was used to adjust the intra-correlation effect for the patients who had multiple thrombotic events. This procedure is a repeated measures analysis for correlated dichotomous outcomes (not adjusted for length of follow-up). All tests of significance were two-sided, and differences were considered statistically significant when the P value < 0.05. All data were expressed as means ± SD. SAS version 6.12 and SAS PHLEV macro were used for all analyses.

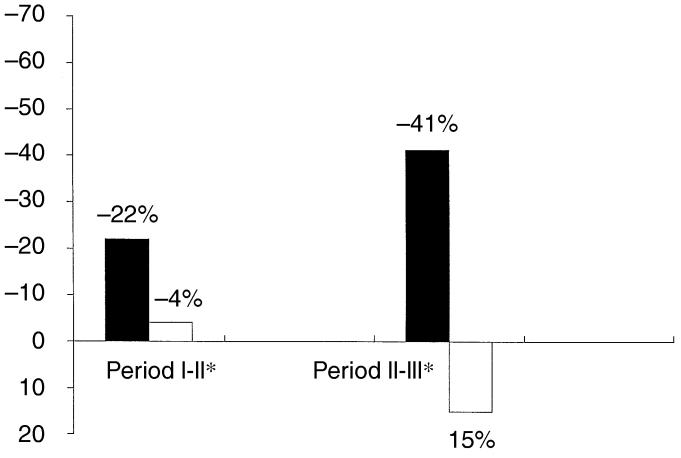

Fig. 1. Vascular access blood flow changes between study period I to II and study period II to III. $P < 0.05$ thrombosis vs. no thrombosis for each period of observation, respectively. Symbols are: (■) thrombosis; (□) no thrombosis.

RESULTS

A total of 34 thrombotic events in 95 accesses were documented (0.24 events/access/year) through the total length of the study. Thirty (88%) thrombotic events were documented in PTFE grafts and 4 (12%) episodes of thrombosis occurred in AVF. The mean VABF for all accesses for the 18 months period of follow-up was 1227 ± 700 ml/min (range 243 to 4441). When the average blood flow of all accesses were calculated, there was no numerical and/or statistical difference in blood flows at the three observation periods (1243 ± 729 ml/min, range 243 to 3867 for the first period of observation, 1185 ± 731 ml/min, range 284 to 4441 during the second period of observation, and 1253 ± 639 ml/min, range 374 to 3340 for the third period of observation).

The data were further analyzed for comparison between accesses that subsequently thrombosed versus those that did not thrombose. During the first period of observation VABF was 1205 ± 277 ml/min for those accesses that subsequently thrombosed versus 1579 ± 703 ml/min for those that did not thrombose ($P < 0.01$). Similarly, for the second period of observation VABF was 910 ± 381 ml/min for the accesses that had thrombotic events versus 1301 ± 811 ml/min for those that had no events ($P < 0.01$). For the study period III, the VABF was further reduced to 661 ± 276 ml/min for the accesses that had thrombotic events. Those that did not thrombose had a mean VABF equal to 1287 ± 638 ml/min ($P < 0.05$).

Figure 1 represents the percent changes of VABF between baseline and the subsequent period of observation for the accesses that thrombosed versus those that did not thrombose over the ensuing 22 weeks. The accesses that thrombosed had a 22% decrease in blood flow between the first period of observation and the second ($P < 0.05$), and 41% decrease between the second and third periods of observation ($P < 0.05$). In contrast, accesses that did not thrombose had a 4% decrease in VABF between observation period one to two and a 15% increase between observation period two to three.

Figure 2 depicts a diagram of the estimated relative risk ratio for thrombosis by 5% decrements of vascular access blood flow over time up to 50% decrease in VABF. When accesses with no decrease in blood flow were considered as a reference range (relative risk 1.0), there was a highly significant exponential increase in the risk of thrombosis for each blood flow decrement of 15% or higher. Specifically, for accesses with up to a 15% decrease in access blood flow, the relative risk of subsequent thrombosis within the next 22 weeks is estimated to be 4.4 times higher (95%, confidence interval 1.08 to 18.11) as compared to those accesses that have no change in blood flow. When access blood flow decreased by more than 25% the estimated relative risk of thrombosis increased approximately sevenfold (95%, confidence interval 1.51 to 30.94). The relative risk of thrombosis was 35-fold higher (95%, confidence interval 4.67 to 257.57) when access blood flow was reduced by 50% compared to those with no decrement in VABF.

Since it has been suggested that native fistulas and PTFE grafts have different thrombosis patterns, that is, lower thrombosis rates at lower access blood flows in native fistulas, we analyzed the data after adjusting for access type. The results showed that based on the decline in access blood flow, the estimated relative risk of thrombosis was the same even with adjustment for each access type without any numerical or statistical difference.

In Figure 3, the Kaplan-Meier plot of the probability of access survival is displayed for the group of accesses that had no change in access blood flow, compared to those

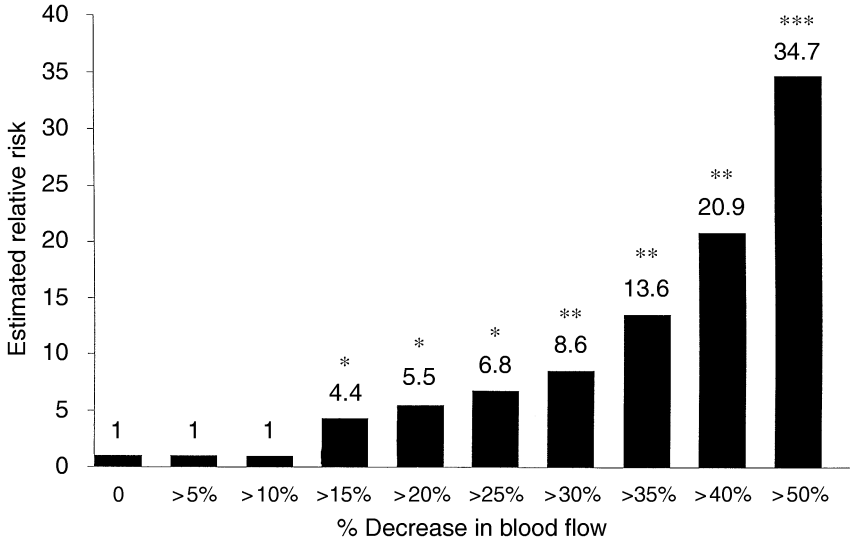

Fig. 2. Relative risk of thrombosis within the subsequent 12 weeks by changes in access blood flow at six months intervals measured by ultrasound dilution. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Reference group (relative risk = 1) is the first group with no decrease in blood flow.

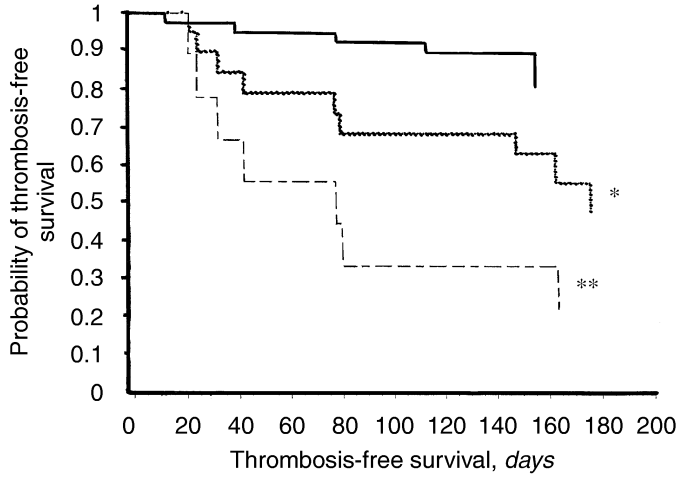

Fig. 3. Kaplan-Meier plot of probability of thrombosis free access survival according to the percent decrease in vascular access blood flow over a six month interval versus no change in vascular access blood flow. Symbols are: (continuous line) no change in VABF; (dotted line) up to 25% decrease in VABF; (dashed line) up to 40% decrease in VABF; $^{*}P = 0.02$, $^{**}P = 0.001$.

accesses who showed a reduction in VABF grouped in three different percent changes. As can be seen, the majority of thrombotic events occurred between day 10 through day 90 following the VABF measurements. Specifically, at day 90 the probability of patency for accesses with no change in VABF was 92%. When there was a decrease in VABF of as much as 25%, the probability of patency at 90 days was 74% ($P < 0.05$). Likewise, for those accesses that had a decrease in VABF equal or higher than 40% the predicted patency rate was 33% within this same 90 day interval ($P < 0.01$).

DISCUSSION

The results of this prospective study demonstrate that a temporal decrease in hemodialysis vascular access blood flow, detected through serial measurements, is a powerful predictor of vascular access thrombosis within the subsequent 24 weeks. Even though sequential access blood flow screening has been recently proposed in the National Kidney Foundation-Dialysis Outcomes Qualitative Initiative guidelines [19] as the appropriate screening tool for vascular access failure, to our knowledge this is the first study to provide evidence in support of this opinion-based recommendation.

It is important to note that the authors, as well as several others have reported the importance of absolute values of VABF as an indicator of subsequent thrombotic events in hemodialysis patients, especially when VABF is less than 800 ml/min [15, 20, 21]. However, approximately 20% of accesses with initial blood flows above 1000 ml/min do thrombose over the following three to six months. The results of this study strongly suggest that consecutive measurements of VABF is a reliable and more predictive method for detecting incipient vascular access failure. Our analysis shows that sequential measurements of VABF have a much larger predictive power for thrombosis; for example, the estimated relative risk increases up to 35 times when a 50% decrease in blood flow occurs compared to accesses with no change in blood flow.

Several studies have demonstrated that stenosis at the efferent venous anastomosis of the graft accounts for approximately 70% of thromboses in PTFE grafts [22–24]. Venous stenosis is thought to result from progressive narrowing of the vessel lumen over time from the process of myointimal hyperplasia. This results initially in increased resistance to blood flow at the venous anastomosis site and as the intimal proliferation becomes critical, a gradual decrease in intra-access blood flow occurs that predisposes the access to thrombosis due to stasis. The findings in this study are in accordance with the concept that continuous

narrowing in the access along with decreasing blood flow over time is followed by complete occlusion due to thrombosis [25].

The importance of this study can be evaluated in the context of the significant economic and morbidity burdens that result from those vascular accesses with unexpected or sudden thrombosis that are generally detected when a CHD patient presents for dialysis. This often requires a hospital admission, placement of a temporary catheter for dialysis, subsequent angiogram of the access and follow up angioplasty and/or surgical repair or placement of a new access. Recent evidence suggests that when combined with therapeutic interventions, prospective screening and detection of dysfunctional hemodialysis access grafts may improve the long term patency of the access [3, 5]. However, such studies have been hampered by the lack of predictive tests with sufficient sensitivity and specificity. This study suggests that moderate reduction of VABF is associated with a high likelihood of access thrombosis in the short term. Thus, the general availability of this test would allow radiological (angioplasty) and/or surgical intervention before the onset of thrombosis, leading to significant savings in hospitalizations, procedure costs and decreased patient morbidity.

An important issue that has not been clearly delineated by this study is the optimal frequency of sequential screening in order to detect the access at risk. In this study where measurements of vascular access flow were made every six months, the majority of thrombotic events occurred within 2 to 12 weeks after a measured ($>22\%$) decrease in access flow. Therefore, at present, with the available methods of access screening, we propose that monthly or bimonthly measurements should be performed for optimal detection. However, further studies will be needed to define the optimal interval between measurements that provides early detection of increased risk of thrombosis without generating high operational costs of detection that, at present, is not subject to reimbursement. It is also important to note that the ultrasound dilution technique used in this study, although easy to learn, requires well-trained personnel and makes the screening of large patient populations a time consuming and labor intensive task.

An additional and important finding in this study was that relationship between the decline in access blood flow and the estimated relative risk of thrombosis was not influenced by access type. Thus, the results of this study suggest that time dependent changes in access flow are as predictive in native fistulas as in PTFE grafts for subsequent thrombosis, at least in this study population. This is in contrast to the findings based on absolute access blood flow measurements which suggest that native fistulas may function well even at access blood flows below 800 ml/min. This study therefore provides an important new predictor for increased risk of thrombosis in native fistulas (as well as PTFE grafts). It should be noted that the number of native fistulas followed was relatively small in this study and further studies with larger number of accesses are needed to confirm this finding.

In summary, this study has prospectively determined that measurement of VABF plays an important role in the evaluation and detection of PTFE grafts at higher risk of thrombosis, not only through the detection of low VABF but also through serial measurements, by detecting decrements in VABF over time. These tests provide another tool to diagnose access malfunction and support the possibility that early detection and timely correction of underlying problems prior to thrombosis may play a central role in maintaining patency of the vascular access and delivering adequate dialysis therapy.

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